



Neuroblastoma: MIBG Imaging and New Tracers

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Neuroblastoma is an embryonic tumor of the peripheral sympathetic nervous system, and is metastatic or otherwise high risk for relapse in nearly 50% of cases, with a long-term survival of <40%. Therefore, exact staging with radiological and nuclear medicine imaging methods is crucial for finding the adequate therapeutic choice. The tumor cells express the norepinephrine transporter, which makes metaiodobenzylguanidine (MIBG), an analogue of norepinephrine, an ideal tumor-specific agent for imaging. On the contrary, MIBG imaging has several disadvantages such as limited spatial resolution, limited sensitivity in small lesions, need for two or even more acquisition sessions, and a delay between the start of the examination and result. Most of these limitations can be overcome with positron emission tomography (PET) using different radiotracers. Furthermore, for operative or biopsy planning, a combination with morphological imaging methods is indispensable. This article would discuss the therapeutic strategy for primary and follow-up diagnosis in neuroblastoma using MIBG scintigraphy and different new PET tracers as well as multimodality imaging.

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Introduction

Neuroblastoma is the most common extracranial solid malignancy in pediatric patients (approximately 8% of pediatric malignancies) and remains, despite treatment intensification, responsible for approximately 15% of cancer deaths in children.¹⁻⁴ It is an embryonic tumor, arising from the neural crest cells, which give rise to the adrenal medulla and the sympathetic nervous system.⁵ The tumor is most frequently situated in the adrenal gland or anywhere else along the sympathetic nervous system chain.¹ At diagnosis, roughly 50% of patients have distant hematogenous metastases.⁶ Neuroblastoma presents a great heterogeneity concerning clinical behavior and survival rates; therefore, staging is crucial to choose the appropriate treatment.⁷ There is strong evidence that initial staging of neuroblastoma (NB) remains decisive regarding risk-stratification to choose the most appropriate treatment option.^{3,8} Imaging of NB consists of sonography, computed tomography (CT), magnetic resonance imaging

(MRI), and radionuclide examinations such as scintigraphic bone scanning, metaiodobenzylguanidine (MIBG) scintigraphy, positron emission tomography (PET) with different tracers (primarily fluorodeoxyglucose [FDG]), and recently hybrid imaging (PET/CT, SPECT/CT, and PET/MRI).⁹⁻²¹ The therapeutic spectrum depends upon clinical stage and consists of supportive care with no treatment (stage IVS), definitive excision if possible, or chemotherapy before and after surgery partially combined with total-body irradiation and MIBG therapy, followed by autologous bone marrow transplantation.^{4,6,22,23}

Imaging strategies with different nuclear medicine methods and a multimodality approach in staging and following up patients with NB is the subject of the present review.

MIBG Scintigraphy

Radiolabeled MIBG was originally developed in the late 1970s as a norepinephrine (NE) analogue for imaging of the adrenal medulla.^{24,25} In the quantities administered for diagnostic imaging, uptake of MIBG is mediated primarily by the NE transporter located on the surface of sympathetic neurons.^{26,27} Based on this mechanism of uptake, MIBG has proven an effective agent for scintigraphic imaging of tumors that arise from the embryonologic precursors of the sympathetic

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nervous system, particularly the neural crest tumors NB and pheochromocytoma.^{28,29} MIBG labeled with iodine-131 (¹³¹I) was developed by Wieland et al^{25,30,31} and Sisson et al³² at the University of Michigan as an imaging agent for tissues and tumors of the sympathetic nervous system, originally for the localization and treatment of pheochromocytomas.³³ During the past 25 years, both ¹²³I-MIBG and ¹³¹I-MIBG have been extensively used in research and clinical imaging of NB.^{28,29,34}

The superiority of ¹²³I over ¹³¹I-labeled MIBG for the diagnosis has been reported by Shulkin et al.³⁵ Because of its physical properties, ¹²³I offers the possibility to examine patients with both planar or whole-body high-count scans or both, providing a better resolution than ¹³¹I while still allowing the acquisition of late images, up to 48 hours after injection, which may be useful in some cases of well differentiated tumors or equivocal findings on the 24-hour images. Owing to more favorable dosimetric properties, a higher activity of ¹²³I can be administered enabling us to obtain single-photon emission computed tomography (SPECT) acquisitions that may increase sensitivity and provide more precise anatomical localization of the disease especially after co-registration with radiological modalities such as CT-scan or MRI.⁸

Scintigraphy with ¹²³I-labeled or ¹³¹I-labeled MIBG has become a well-established method in the diagnosis and staging of NB³⁶ because of its high specificity, which is reported in the literature to be between 90% and 100%.^{22,33,37}

Reasons for false-negative studies are not entirely elucidated—it may be related to modifications of the active uptake mechanism owing to differentiation of tumor cells or

pharmacologic interference.³⁸⁻⁴⁰ Pharmacological interference is probably the most frequent cause of a false-negative study. If no drug interference can be incriminated, tumor cell differentiation and maturation could lead to a decrease of MIBG uptake and be responsible for a false-negative examination.⁸ This has been described in children with ganglioneuroblastoma, where the ganglioneuroma elements were predominant, suggesting that uptake is influenced by histology and the degree of tumor cell maturation, whereas no relationship with the secretion of catecholamines could be assessed.³⁸ Biasotti et al³⁶ reported 16 of 196 children (8%) with proven localized ($n = 88$) or disseminated ($n = 108$) NB who had a complete negative MIBG scan at diagnosis, and found no correlation with histopathology, biological factors or stage of the disease. On the contrary, Fendler et al could show that in pediatric patients with peripheral neuroblastic tumors, strong ¹²³I-MIBG uptake indicates unfavorable histopathology (UH). High uptake was seen in NBs and in tumors with a high mitotic activity.⁴¹

In the 55 patients, 61 lesions were evaluated with ¹²³I-MIBG SPECT and corresponding histopathological findings were reviewed (11 ganglioneuroma, 11 ganglioneuroblastoma, and 39 NB). Tumor-to-liver count-rate ratio (TLCRR) was significantly higher in the NB group (mean TLCRR = 2.7) than in the ganglioneuroblastoma group (mean TLCRR = 1.0) and ganglioneuroma group (mean TLCRR = 0.7) at the time of primary diagnosis ($P < 0.001$) and at follow-up ($P = 0.039$). Intense ¹²³I-MIBG uptake was found in tumor tissue with a high mitotic activity after treatment (Fig. 1). Four

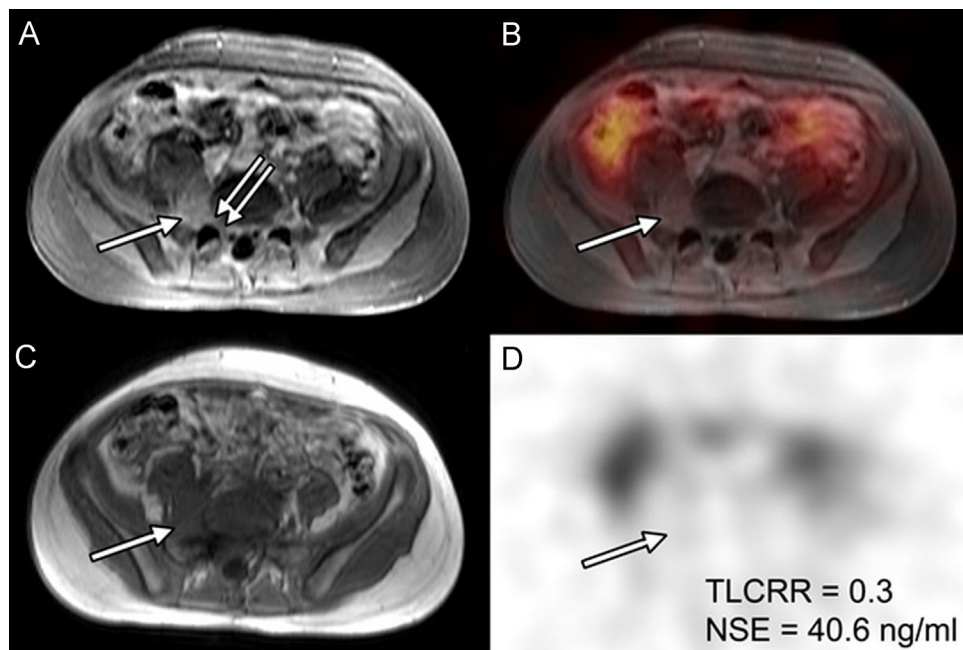


Figure 1 True positive prediction of unfavorable histopathology (UH) by combined TLCRR/NSE criteria in a 14-year-old boy. T1-weighted axial MRI with (A) and without (C) contrast enhancement, ¹²³I-MIBG SPECT (D) and fused SPECT/MRI (B) of the lower abdomen are shown. Tumor is depicted as contrast-enhancing lesion in a paravertebral location (A, arrow) with infiltration of the L5 neuroforamen (A, double arrow). Tumor-to-liver count-rate ratio (TLCRR) was < 2.1 (D, false negative). Serum neuron-specific enolase (NSE) level was > 25.8 ng/mL (D, true positive). Combined analysis resulted in a true positive finding for UH. Undifferentiated neuroblastoma was confirmed by histopathology following surgery. (Color version of figure is available online.)

ganglioneuromas (36%), three ganglioneuroblastomas (27%), and six NBs (15%) were ^{123}I -MIBG-negative.⁴¹

Furthermore, it could be shown that strong ^{123}I -MIBG uptake and high serum level of neuron-specific enolase (NSE) were each predictive of UH. Combined analysis of both parameters improved the prediction of UH in patients with neuroblastic tumor (Figs. 1 and 2). MRI parameters and urine catecholamine levels did not predict UH.⁴²

Of 47 patients, 34 had UH based on the International Neuroblastoma Pathology Classification. TLCRR and serum NSE both predicted UH with moderate accuracy. Optimal cutoff for TLCRR was 2.0, resulting in 68% sensitivity and 100% specificity (AUC-ROC = 0.86, $P < 0.001$). Optimal cutoff for NSE was 25.8 ng/mL, resulting in 74% sensitivity and 85% specificity (AUC-ROC = 0.81, $P = 0.001$). Combination of TLCRR-NSE criteria reduced false-negative findings from 11/9 to only 5, with improved sensitivity and specificity of 85% (AUC-ROC = 0.85, $P < 0.001$).⁴²

In lesion-based evaluations, the main cause for false-negative MIBG findings are bone respectively bone marrow metastases leading to reduced overall sensitivities between 60% and 70%.^{37,43,44}

On the contrary, one must be aware of the physiological distribution of MIBG to avoid false-positive results. Some organs (heart and salivary glands) show quite high MIBG uptake because of their sympathetic innervation, while other systems (urinary tract, gastrointestinal system) represent

excretion routes of the tracer.⁴⁵ Most of the false-positive MIBG findings are due to a nonspecific radioactive accumulation in urinary tract, or gastrointestinal structures or both, and not to specific MIBG uptake by nonneuroblastic cells.^{44,46-50}

A major disadvantage of planar ^{123}I -MIBG scintigraphy is represented by the lack of anatomical information and the relatively poor resolution when compared to radiological examinations. Several groups have investigated the added value of SPECT in comparison with planar images.⁵¹⁻⁵³ Gelfand et al⁵³ reported on 35 studies performed in 25 children with NB and observed no significant increase in the number of lesions detected by SPECT. Rufini et al⁵² observed more lesions with SPECT than with planar images, but also mentioned that specificity of the examination could be decreased owing to liver inhomogeneity which may be interpreted as false-positive or equivocal lesions. Both studies observed that SPECT was able to give more information on localization and extent of the lesions, but did not effect staging of the disease.

In an attempt to quantify the bulk of metastatic disease in patients with NB, semiquantitative scoring systems have been proposed. The most commonly adopted is the Curie scoring system, which is used by the Children's Oncology Group (COG)⁵⁴: this system divides the skeleton in nine compartments. A 10th compartment is used for lesions in the soft tissues, including the primary tumor. The extension score for

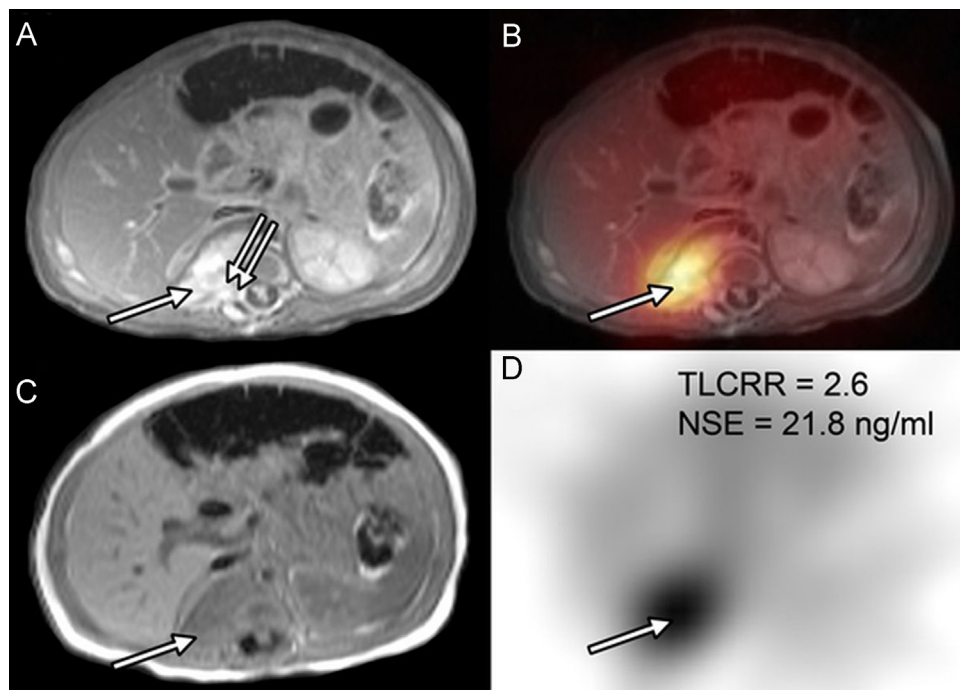


Figure 2 True positive prediction of unfavorable histopathology (UH) by combined TLCRR/NSE criteria in a 4-month-old girl. T1-weighted axial MRI with (A) and without (C) contrast enhancement, ^{123}I -MIBG SPECT (D) and fused SPECT/MRI (B) of the abdomen are shown. Images show a lesion with contrast enhancement (A, arrow) and infiltration of the L2 neuroforamen (A, double arrow). Tumor-to-liver count-rate ratio (TLCRR) was > 2.1 (D, true positive). Serum neuron-specific enolase (NSE) level was < 25.8 ng/mL (D, false negative). Combined analysis resulted in a true positive finding for UH. Poorly differentiated neuroblastoma was confirmed by histopathology following surgery. (Color version of figure is available online.)

this method is graded as: 0 = no metastatic involvement; 1 = 1 site of involvement per segment; 2 = more than 1 site per segment; and 3 = diffuse involvement (>50% of the segment).

As an alternative, the SIOOPEN method divides the skeleton in 12 anatomic segments.⁵⁵ The extension score for this method is graded as follows: 0 = no sites per segment; 1 = one discrete site per segment; 2 = two discrete sites per segments; 3 = three discrete lesions; 4 ≥ 3 discrete foci or a single diffuse lesion involving <50% of the segment; 5 = diffuse involvement of 50%-95% of the segment; and 6 = diffuse involvement of the entire segment.

With the use of these semiquantitative scoring systems it could be shown that they allow prediction of outcome in patients with stage 4 NB.^{55,56} In this concern, Decarolis et al⁵⁵ could show that Curie and SIOOPEN scoring systems reveal comparable results regarding the potential of predicting outcome.

On the contrary, Morgenstern et al recently analyzed data from the International Neuroblastoma Risk Group database for 2250 patients with stage 4 disease treated from 1990-2002.⁵⁷ Metastatic burden was assessed using a “metastatic site index” (MSI), a score based on the number of metastatic systems involved. Overall, involvement of bone marrow, bone, lung, central nervous system, or other sites was associated with worse outcome.⁵⁷ For patients aged ≥18 months, involvement of liver had the greatest effect on outcome and was associated with tumor MYCN amplification and adrenal primary and lung metastases. Increased MSI was associated with worse outcome and higher baseline ferritin-lactate dehydrogenase. Furthermore, they explored the effect of initial treatment approach on these associations.⁵⁷ Limiting the analysis to patients allocated to protocols including stem cell transplant (SCT), there was no longer an association of outcome with metastatic involvement of any individual system or increasing MSI. Thus, treatment escalation with SCT (and the addition of differentiating agents to maintenance therapy) appears to have provided maximal benefit to patients with greatest metastatic disease burden.⁵⁷

¹²³I-MIBG scintigraphy still represents the most important functional imaging available to study patients affected by NB. This diagnostic tool is the “cornerstone” in the assessment of NB at initial diagnosis, staging, restaging, and detection of disease relapse.⁵⁸ In addition, indication for MIBG therapy using a high activity of ¹³¹I-MIBG is depending on the result of diagnostic ¹²³I-MIBG scintigraphy.

Nevertheless, ¹²³I-MIBG scintigraphy commonly contemplates planar acquisitions, necessitates adequate patient preparation, and requires correlation with radiological examinations (ie, ceCT or MRI) in most of the cases. SPECT or SPECT/CT acquisitions should be obtained although these modalities are time consuming, tend to cover only a limited field of view, and increase the rate of patient sedation. However, spatial resolution remains limited and the sensitivity in detecting small lesions often is poor.

In this context, introduction of other complementary PET tracers for correct identification of NB lesions in clinical practice seems to be very useful.

In recent years, different types of PET tracers have been used in NB and compared with ¹²³I-MIBG.⁵⁹ However, questions remain regarding the role of PET/CT in NB.

Positron Emission Tomography

Despite the high diagnostic accuracy of MIBG imaging, there are several disadvantages of this modality such as limited spatial resolution, limited sensitivity in small lesions, need for two or—in the case of SPECT—even more acquisition sessions, and a delay between the start of the examination and result. Furthermore, in most of the cases, MIBG imaging is not sufficient for operative or biopsy planning. Most of these disadvantages can potentially be overcome with PET because of its higher spatial resolution and the possibility of a whole-body tomography vs SPECT with a limited field of view. PET or PET/CT is completed in one examination within 30-60 minutes after injection vs ¹²³I-MIBG scintigraphy and SPECT or SPECT/CT requiring at least 18-24 hours to achieve tumor-to-background ratios adequate for imaging. The resulting shorter scanning time of PET has the potential for reducing the number of sedations.

¹⁸F-FDG PET/CT

As for other malignancies, NB is often characterized by a high ¹⁸F-FDG uptake. Although data about the role of ¹⁸F-FDG in NB are limited and no prospective multicentric studies have been conducted, ¹⁸F-FDG PET/CT represents an important and widely available alternative to ¹²³I-MIBG scan, especially in case of non-MIBG concentrating NB. However, 2011 guidelines for imaging and staging of NB did not clearly recognize the diagnostic role of ¹⁸F-FDG PET/CT. The authors underlined that the feasibility of PET/CT in young children, the associated radiation exposure, and the higher cost in addition with those of MIBG scanning, may explain the limited use of this technique.⁶⁰ Indeed, one recent Cochrane review on imaging for diagnosing NB⁶¹ included only one study directly comparing ¹²³I-MIBG scintigraphy and ¹⁸F-FDG PET¹² and reported that ¹⁸F-FDG PET/CT seems to be slightly more sensitive than ¹²³I-MIBG scan (100% vs 92%). However, this study¹² encompassed only patients at the first staging with already proven NB. In this context, no significant difference in sensitivity between the diagnostic methods have been reported and no specificity calculation was feasible.

Irrespective from this interesting but stringent review,⁶¹ some more practical considerations about the use of ¹⁸F-FDG PET/CT in NB may be done.

In particular, *at the time initial staging*, it was found that ¹⁸F-FDG PET identified disease sites in stage 1 and 2 NB better than ¹²³I-MIBG, and detected more sites of primary tumors or loco-regional metastases.¹² Moreover, ¹⁸F-FDG PET/CT better detected sites of disease in stages 3 and 4 when tumors did not accumulate ¹²³I-MIBG or did so only weakly.¹² In addition, ¹⁸F-FDG PET/CT could provide important information about disease extension in chest, abdomen and pelvis, and should be used when CT or MRI seem to show more extensive disease

than that revealed by ^{123}I -MIBG scan.¹² However, ^{123}I -MIBG seems to be superior to ^{18}F -FDG PET/CT in staging high-risk NB (eg, stage 4), owing to its better detection of metastases in bone and bone marrow, which are the most frequent sites of disease progression.^{11,12} This situation may happen during the initial chemotherapy or under granulocyte-colony stimulating factor, when bone marrow FDG uptake may mask or mimic metastatic disease, thus reducing the sensitivity of ^{18}F -FDG PET techniques.^{11,12} Another limitation of ^{18}F -FDG PET/CT is the normal high uptake of FDG in the brain, which makes this technique less effective for imaging cranial vault lesions.¹¹ Accordingly, Taggart et al¹¹ reported that MIBG imaging was significantly more sensitive than ^{18}F -FDG PET imaging in detecting bone lesions, both in entire skeleton and in the cranial vault.

When detection of NB relapse is considered, ^{123}I -MIBG proved superior to ^{18}F -FDG in depicting the bone-bone marrow component of disease.^{11,62} This is a critical point in relapsing patients, because soft tissue involvement is expected to be low and bone and bone marrow disease results more prevalent.

However, given the fact that ^{18}F -FDG can identify disease in ^{123}I -MIBG-negative lesions, it might serve as a complementary imaging modality in selected patients (Fig. 3). In this setting, ^{18}F -FDG was able to detect soft tissue disease not seen on ^{123}I -MIBG imaging, even in patients who had ^{123}I -MIBG-positive lesions in different sites.¹¹ Although it has been hypothesized that ^{18}F -FDG might be better in detecting liver

lesions due to the physiologic uptake of ^{123}I -MIBG by liver, this hypothesis was not confirmed by others.¹⁸

During follow-up, when suspected NB relapse is the issue, correct choice of functional imaging modalities seems to be crucial. There are reports of lesions that had been ^{123}I -MIBG-positive at the initial diagnosis and became negative when the disease relapsed or vice versa (negative at initial diagnosis, positive at relapse).^{13,18,63}

^{18}F -FDG imaging is helpful during follow-up when ^{123}I -MIBG scan/SPECT yield discrepant or inconclusive findings.⁶⁴ In this particular setting, the sensitivity values of ^{123}I -MIBG scintigraphy and ^{18}F -FDG PET were 50% and 78%, respectively, and their specificity values were 75% and 92%, respectively.⁶⁴ Interestingly, in the article by Melzer et al, there was no correlation between tumor size and false-negative results on ^{123}I -MIBG scintigraphy and ^{18}F -FDG scan. In false-negative findings, the mean lesion diameter was 1.7 cm on ^{123}I -MIBG scintigraphy and 1.6 cm on ^{18}F -FDG PET/CT. This finding confirms how the tracer uptake mechanisms influence the diagnostic accuracy, independently from the spatial resolution of PET and SPECT imaging.

^{123}I -MIBG scintigraphy at the end of initial induction chemotherapy is the most important cornerstone in *treatment response* assessment of high-risk NB. ^{123}I -MIBG has proved to be a sensitive and specific biomarker at this time,⁶⁵ and the persistence of disease documented by ^{123}I -MIBG scan after induction therapy is considered an unfavorable prognostic factor.^{54,66}

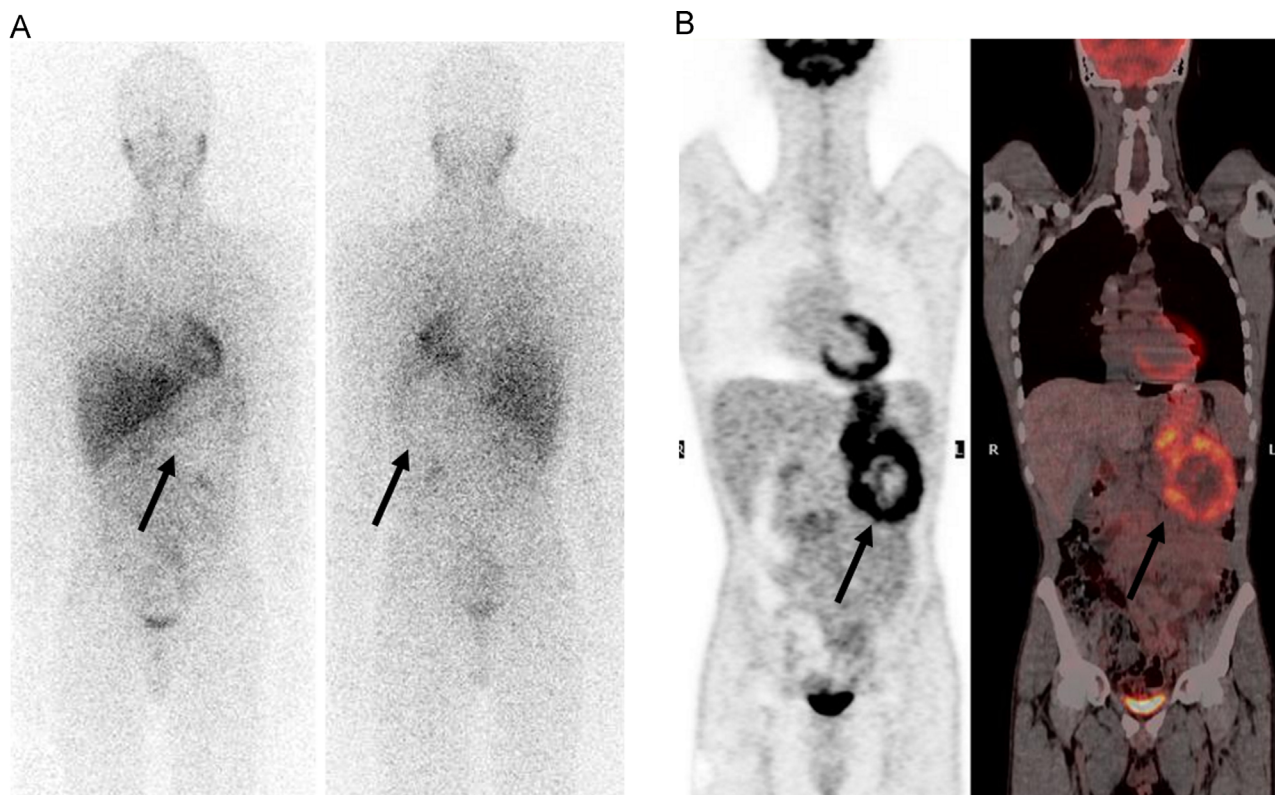


Figure 3 A 6-year-old child affected by NB. The big abdominal mass, negative on ^{123}I -mIBG (A), was well depicted by ^{18}F -FDG PET/CT (black arrows). The distribution of the tracer was inhomogeneous owing to prevalent intratumoral necrotic phenomena. (Color version of figure is available online.)

However, ^{18}F -FDG PET/CT imaging is able to monitor treatment response, in patients with ^{123}I -MIBG-negative tumors.⁶⁷ In this setting, it has been demonstrated that most of NB are able to concentrate ^{18}F -FDG both before and after cytoreductive therapy.⁶⁸ Kushner et al⁶⁹ reported that ^{18}F -FDG PET/CT findings correlated well with disease status, and were able to properly define treatment effects and disease evolution. ^{123}I -MIBG scintigraphy, however, is more sensitive than ^{18}F -FDG PET/CT in assessing the response to ^{131}I -MIBG therapy in patients with relapsed NB.⁷⁰ On the contrary, ^{18}F -FDG-PET/CT displayed greater sensitivity than ^{123}I -MIBG in detecting soft tissue lesions, and it was reported that ^{18}F -FDG PET/CT becomes negative more often than ^{123}I -MIBG scans after treatment.¹¹ The principal limitation of ^{18}F -FDG PET/CT remains the nonspecific bone marrow uptake during chemotherapy or administration of granulocyte-stimulating factor. This problem can be overcome by scheduling ^{18}F -FDG PET just before the course of chemotherapy.⁵⁹

It is important to determine the prognostic implications of ^{123}I -MIBG-positive residual NB tumors.

If ^{18}F -FDG PET/CT is negative but ^{123}I -MIBG scan is still positive, biopsy might confirm whether the tumor has matured or has only been temporarily stunned for metabolic activity.^{11,59} In this concern, one recent report confirmed the usefulness of ^{18}F -FDG PET/CT in predicting response to a differentiation agent, such as 13-cis-retinoic acid, in one patient affected by residual disease after myeloablative chemotherapy.⁷¹ Thus, the combined use of ^{18}F -FDG PET/CT and ^{123}I -MIBG scintigraphy might better depict residual disease in this clinical scenario, and thus adding important information, especially before SCT.⁵⁹

^{18}F -FDG has been proposed as an important prognostic biomarker in some different malignancy,⁷²⁻⁷⁵ and also in NB ^{18}F -FDG PET/CT seems to have an important *prognostic role*.⁵⁹ Papanthasiou and colleagues reported that an increased tumor metabolic activity, expressed by standardized uptake value (SUV_{max}) and the presence of extensive ^{18}F -FDG-avid metastases have been identified as poor prognostic factors associated with decreased survival. In addition they showed that a pattern of increased ^{18}F -FDG uptake, exceeding the tumor avidity for ^{123}I -MIBG, corresponded to more aggressive disease and worse outcome.⁶²

Similar conclusions on a more selected (ie, drug naïve patients) and greater population of NB patients, have been recently reported by Lee et al.⁷⁶ They showed that the FDG uptake expressed by SUV_{max} of the primary tumor lesion and metastatic lesions normalized for mean SUV of normal liver tissue was, in a multivariate analysis considering all the principal prognostic factors, the only one parameter significantly associated to overall survival.⁷⁶

Liu et al⁷⁷ recently observed an association between high ^{18}F -FDG uptake of NB primary tumor and the most unfavorable genomic types such as MYCN amplification or segmental chromosomal alteration or both. The SUV_{max} of FDG were significantly higher in patients with high-risk features, including older age, stage 4, MYCN amplification, and anatomical image-defined risk factor.⁶⁰ In addition, they found that the primary tumor metabolic pattern characterized by high FDG

uptake ($\text{SUV}_{\text{max}} > 3.31$) and low catecholamine metabolism (expressed by a low DOPA uptake) was directly associated to disease progression.⁷⁷

^{18}F -DOPA PET/CT

From the functional point of view, NB is characterized by an increased metabolism of catecholamines, which determines its ability to produce biologically active hormones such as NE and some of its precursors, such as DOPA and dopamine.^{58,78}

^{18}F -3,4-dihydroxyphenylalanine (DOPA) is a precursor of dopamine and a precursor of catecholamines. This molecule is actively transported into cells through the transporter system of large neutral amino acids (LAT1) and then converted into dopamine by the enzyme amino acid decarboxylase (AADC).⁷⁹ Dopamine is then stored within the intracellular vesicular storage system and converted into NE and epinephrine.⁸⁰ ^{18}F -DOPA is probably the most promising PET alternative to ^{123}I -MIBG in neural crest tumors,⁵⁹ because of its ability to follow the metabolism of catecholamines,^{58,78} and published data^{81,82} seem to support this hypothesis.

Two studies have compared the diagnostic role of ^{18}F -DOPA PET/CT with that of ^{123}I -MIBG scintigraphy in NB.^{83,84} Both studies showed that most of NB lesions are characterized by a specific DOPA uptake and that the pathological distribution of DOPA was similar to that of ^{123}I -MIBG (Fig. 4). Overall, ^{18}F -DOPA PET/CT had a very high sensitivity (DOPA 90% vs MIBG 56%) and accuracy (DOPA 90% vs MIBG 57%), significantly higher ($P < 0.001$) than that of ^{123}I -MIBG scintigraphy.⁸⁴ Nevertheless, both studies did not report any significant difference in specificity (DOPA 75% vs MIBG 62%).

Interestingly, Piccardo et al reported a significant difference in sensitivity between ^{18}F -DOPA and ^{123}I -MIBG scintigraphy in case of small soft tissue lesions at recurrence (84% vs 34%, $P < 0.001$) and in case of bone marrow localizations (96% vs 71%, $P < 0.001$), especially for lesions < 15 mm.⁸⁴

In addition, the authors showed that the overall high accuracy of ^{18}F -DOPA PET/CT influenced patient management and treatment decisions, in comparison with all available data and the initial MIBG report, in 6 of 19 patients (32%) and in 9 of 28 paired scans (32%).⁸⁴

Only one study from Lopci et al⁸⁵ compared ^{18}F -DOPA PET/CT with CT and MRI.

They documented a very high sensitivity for ^{18}F -DOPA PET/CT in detecting NB tumor lesions; moreover, they found for ^{18}F -DOPA PET/CT a significantly higher sensitivity, specificity and accuracy compared to those of MRI and CT. On the lesion-based analysis ^{18}F -DOPA PET and CT/MR showed the following sensitivity, specificity, NPV, PPV, and accuracy rates of 90.6%, 90%, 73.5%, 96.9%, and 90.5% vs 47.5%, 27.5%, 13.1%, 69.5%, and 43% ($P < 0.001$), respectively. When comparing ^{18}F -DOPA PET/CT with CT and MRI in different sites of disease, the authors found that PET had a significantly higher detection rate than CT/MRI in disclosing NB localization in bone and bone marrow (90% vs 7%), in lymph nodes (94% vs 72%) and in soft tissue recurrences (100% vs 11%). No difference in detection rate between PET and CT/MRI was

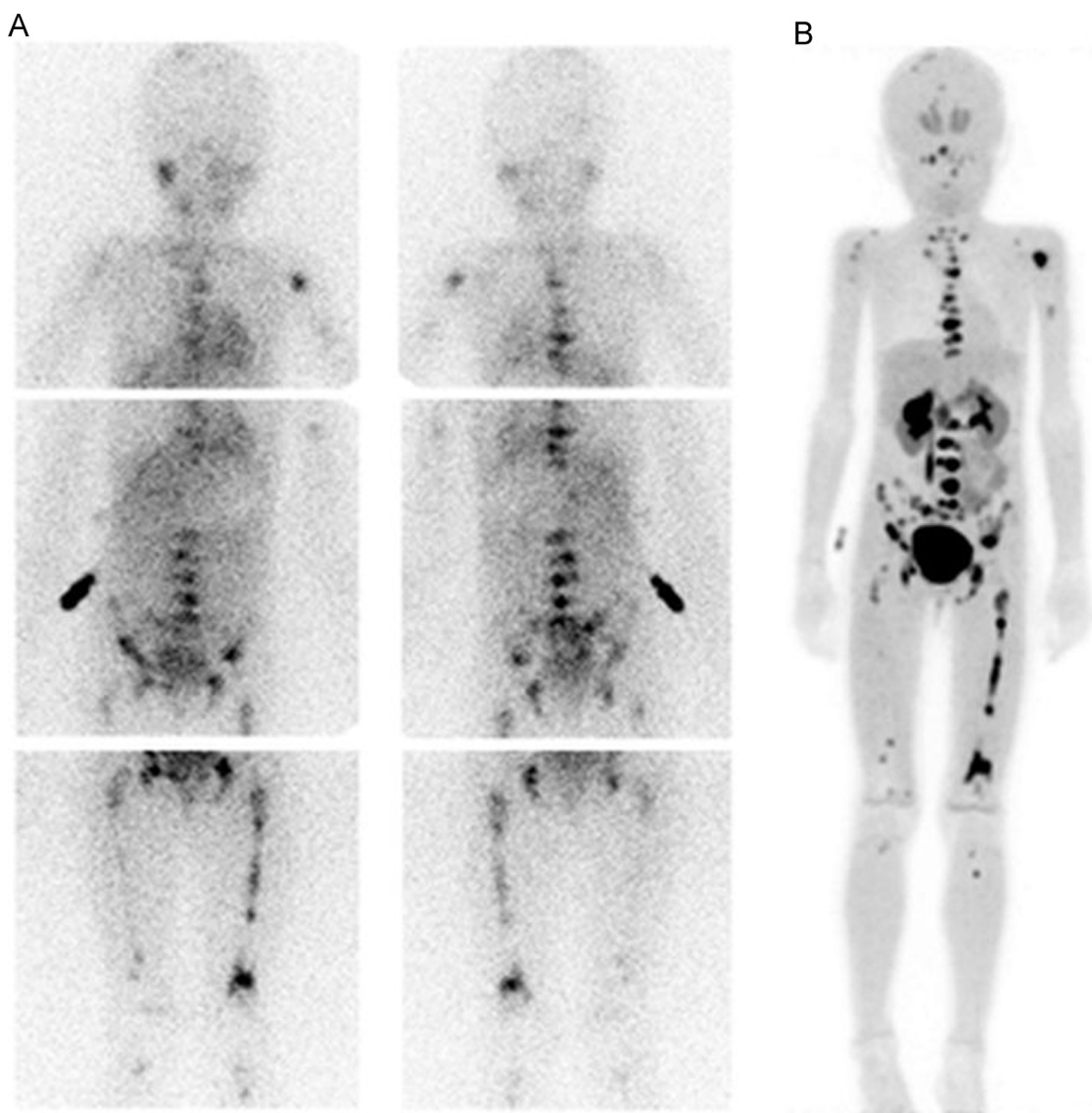


Figure 4 A 6-year-old child affected by diffuse bone and bone marrow NB relapse. ^{123}I -MIBG scan and ^{18}F -DOPA PET/CT showed a very similar pathological distribution of the tracers.

found when primary tumor was taken into account (94% vs 94%). By contrast, CT/MRI showed a significantly higher detection rate than ^{18}F -DOPA PET/CT (100% vs 63%) in identifying NB liver metastases. Some false-positive results of ^{18}F -DOPA PET/CT were found in the liver because of unspecific biliary duct stasis, mimicking metastases.

Lu et al⁸³ directly compared ^{18}F -FDG PET/CT and ^{18}F -DOPA PET/CT in 46 NB lesions. They also compared three different modalities, that is, ^{123}I -MIBG scintigraphy, ^{18}F -FDG PET/CT, and ^{18}F -DOPA PET/CT in 15 NB lesions. They found that ^{18}F -DOPA PET/CT was the most sensitive and accurate method in identifying NB localizations (Fig. 5). On the lesion-based analysis, ^{18}F -DOPA PET/CT and ^{18}F -FDG PET/CT showed the following sensitivity, specificity, and accuracy rates of 97.4%, 87.5%, and 95.6% vs 86.8%, 62.5%, and 82.6%, respectively.

In particular, ^{18}F -DOPA PET/CT, when compared to ^{18}F -FDG PET/CT, showed a better contrast for skull and brain lesions and presented higher sensitivity in detecting neuroblastic primary tumors.⁸³ The ability of ^{18}F -DOPA PET/CT to

detect brain and head-neck NB lesions were more recently confirmed by two studies showing that this imaging technique is able to overcome the intrinsic diagnostic limitations of ^{18}F -FDG PET/CT and ^{123}I -MIBG scan.^{77,86}

As the diagnostic value of ^{18}F -DOPA PET/CT seems to be ascertained by these pilot studies,⁸³⁻⁸⁵ only one study evaluated the prognostic relevance of ^{18}F -DOPA PET/CT in patients affected by NB relapse.⁸⁷ The authors compared ^{18}F -DOPA PET/CT results with ^{123}I -MIBG scintigraphy and other prognostic factors for survival such as age, stage, MYCN status, and the time (from diagnosis) to first relapse.⁸⁸ For better analyzing the prognostic role of ^{18}F -DOPA PET/CT, the authors introduced a new ^{18}F -DOPA PET/CT score to assess the whole-body burden of NB. They called it whole-body metabolic burden (WBMB). The WBMB includes considered two important variables not completely included in the ^{123}I -MIBG score⁵⁴: extent of soft tissue metastases and uptake intensity. The interpatient variability of ^{18}F -DOPA WBMB proved to be higher than that of ^{123}I -MIBG scan scoring

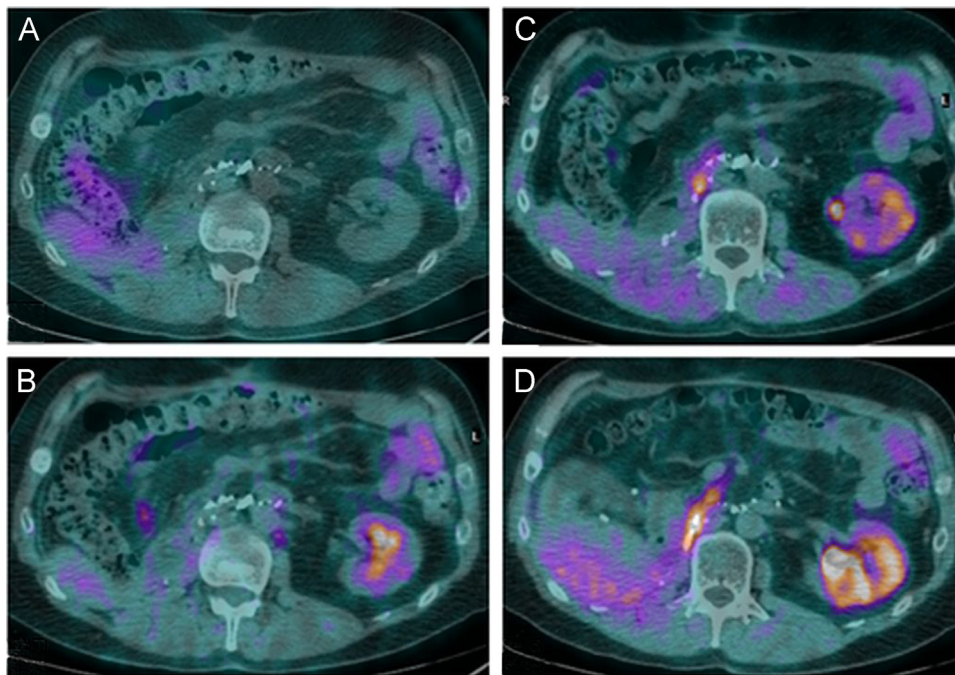


Figure 5 A 40-year-old male affected by right retroperitoneal NB recurrence. No ^{123}I -mIBG and ^{18}F -FDG uptake was detected by SPECT/CT and PET/CT scans in the site of previous surgery (A and B). ^{18}F -DOPA PET/CT showed intense and focal uptake corresponding to a small right paracaval nodule (C). At 2-month follow-up, local recurrence of disease was confirmed by a second ^{18}F -DOPA PET/CT showing a more intense and extended tracer uptake (D). (Color version of figure is available online.)

system. This higher variability in ^{18}F -DOPA WBMB score prompted the reclassification of patients with the same ^{123}I -MIBG score. The authors found that patients with ^{123}I -MIBG score > 3 had a significantly higher risk of disease progression and death than those with ^{123}I -MIBG score < 3 . In addition, patients with ^{18}F -DOPA WBMB > 7.5 displayed a significantly higher risk of disease progression and death than those with ^{18}F -DOPA WBMB < 7.5 .⁸⁷ At multivariate analysis, including all principal prognostic factors at the time of NB relapse, the authors report a significant association between ^{123}I -MIBG score and ^{18}F -DOPA WBMB with respect to progression-free survival. Regarding this, ^{18}F -DOPA PET/CT was better related to progression-free survival than ^{123}I -MIBG scan (HR = 37 vs HR = 17), as its higher score variability was better to stratify the risk of each patient.

The limited experience with the use of ^{18}F -DOPA PET/CT in NB does not allow any final conclusion about the real additional value of this tracer when compared to ^{123}I -MIBG scintigraphy. Further studies on larger populations are required to better validate the promising results reported so far. At the time, ^{18}F -DOPA is not recognized as the tracer of choice in NB and, therefore, only ^{123}I -MIBG scintigraphy together with ^{18}F -FDG PET/CT have been recommended in the last guidelines for imaging and staging of neuroblastic tumors.⁶⁰ In addition, a positive ^{18}F -DOPA PET/CT may not substitute ^{123}I -MIBG scan for establishing ^{131}I -MIBG therapy indication.

However, FDOPA and MIBG have very similar uptake mechanisms; they show the same pathological distribution in soft tissue and bone or bone marrow metastases, thus confirming a common catecholamine pathway.⁵⁹ Moreover,

the physiologic uptake of FDOPA in the pancreas, urinary tract, gallbladder, and epiphyseal plates of the long bones, does not seem to interfere with the PET/CT interpretation. Of course, a careful comparison with morphological imaging is strongly suggested, especially in equivocal findings. An important advantage for ^{18}F -DOPA PET/CT is its rapid and patient-friendly acquisition, especially in dedicated nuclear medicine centers with daily experience of pediatric ^{18}F -FDG PET/CT imaging. From this point of view, ^{18}F -DOPA presents some practical advantage compared to ^{123}I -MIBG.⁸⁷ No specific premedication is required for ^{18}F -DOPA PET. Although premedication with carbidopa is feasible (2 mg/kg, 1 hour before the injection) and it is able to reduce the pancreatic and renal cortex uptake,⁸⁹ diagnostic ^{18}F -DOPA PET/CT for NB studies may be performed without any carbidopa premedication.⁸⁹ Moreover, ^{18}F -DOPA PET data acquisition can be started 60-90 minutes posttracer injection with no difference in tracer distribution and uptake within this time frame.^{83,84} Considering 4 minutes per bed position, the entire acquisition time to cover the whole body (from skull to feet) of a 5-year-old child may range from 28-36 minutes. This aspect dramatically limits the need for sedation compared to ^{123}I -MIBG scintigraphy associated with SPECT.⁹⁰

^{68}Ga -DOTA-TOC PET/CT

Five different types of somatostatin receptors (SSTR) have been discovered so far, and radiolabeled somatostatin analogues have been introduced as an imaging agent for neuroendocrine

tumors in the last decade. NB may be characterized by an overexpression of SSTR, more precisely SSTR types 1 and 2.^{91,92}

Therefore, ¹¹¹In-pentetreotide scintigraphy or, more in general, somatostatin receptor scintigraphy (SRS) have been used for the assessment of NB in the past.^{2,93} However, SRS has not proven to be superior to ¹²³I-MIBG, but, SRS has been considered as a complementary method of ¹²³I-MIBG scintigraphy.

More recently, the rationale of SSTR expression in NB has been considered for the development of potentially promising PET tracers in NB imaging, such as ⁶⁸Ga-DOTA-TOC.⁹⁴ In a small group of patients ($n = 11$), Kroiss et al compared the accuracy of ¹²³I-MIBG scintigraphy with that of ⁶⁸Ga-DOTA-TOC PET/CT in the diagnosis and staging of metastatic pheochromocytoma and NB. On per-lesion-based analysis, sensitivity of ⁶⁸Ga-DOTA-TOC PET/CT was higher than that of ¹²³I-MIBG (97.2% vs 90.7%), and the primary NB lesion was better definable on ⁶⁸Ga-DOTA-TOC PET/CT than on ¹²³I-MIBG imaging. These data are especially relevant for considering indication for a therapy with radiolabeled somatostatin analogues.⁹⁴ Gains et al⁹⁵ used ⁶⁸Ga-DOTA-TATE-PET/CT for diagnosing the presence of disease and ¹⁷⁷Lu-DOTATATE for therapy in eight patients with relapsed or refractory NB. The authors concluded that treatment with ¹⁷⁷Lu-DOTATATE is safe and feasible in children with relapsed or primary refractory high-risk NB. However, as there is already an established therapy method (¹³¹I-MIBG) for NB, more studies are needed to better understand the role of this theranostic approach based on radiolabeled somatostatin analogues.

¹¹C-Hydroxyephedrine PET/CT

¹¹C-hydroxyephedrine (HED) is a catecholamine analogue whose uptake reflects the catecholamine transport, storage, and recycling.⁵⁹ The aromatic portion of HED is less lipophilic than that of MIBG and although HED reveals a closer structural similarity to NE, it is not metabolized as NE. Biodistribution studies in experimental animal and human studies have shown

selective uptake in organs with rich sympathetic innervation, including the heart and adrenal medulla. When HED is labeled with ¹¹C, its distribution can be portrayed in vivo using PET. This agent has been used to map the sympathetic innervation of the heart, and it has been shown that HED is highly concentrated in deposits of pheochromocytoma.⁹⁶⁻⁹⁸

Shulkin et al⁹⁹ first investigated the feasibility and potential utility of ¹¹C-HED PET in localizing NB. The authors reported that HED was promptly accumulated and well-retained by NB. In all seven patients, HED was able to detect NB foci. In comparison to ¹²³I-MIBG requiring at least 18-24 hours for adequate tumor-to-nontumor ratios, early HED tumor uptake is relatively high and, thus, NB can be imaged within minutes. In addition, whole-body exposure to radiation, and especially thyroid exposure is considerably lower on ¹¹C-HED PET as compared to ¹²³I-MIBG.

A drawback reported by these authors, however, was that hepatic and renal uptake were prominent, and liver uptake often exceeded tumor concentration.⁹⁹ In two patients, tumor deposits in the abdomen were better visualized with MIBG scintigraphy due to a relatively lower hepatic accumulation of MIBG than HED. However, HED uptake proved to be higher than that of FDG in one pelvic MIBG-positive metastasis, and ¹¹C-HED PET/CT detected metastases in the skull that had not been visualized by MIBG scan.⁹⁹

Franzius et al¹⁰⁰ compared ¹¹C-HED PET/CT with ¹²³I-MIBG SPECT/CT in tumors of the sympathetic nervous system. Regarding NB, they found that both tracers were able to detect NB localizations with a high sensitivity (96% and 100%, respectively). However, in one patient, ¹¹C-HED PET/CT missed a large abdominal recurrence, which was confirmed on histopathology. Moreover, MIBG uptake proved to be more intense than HED uptake in 10 out of 14 soft tissue metastases. Despite the higher spatial resolution of PET, ¹¹C-HED PET/CT has some disadvantages and limitations in comparison to ¹²³I-MIBG scan. Given the high renal excretion of the tracer during imaging, tumor localization close to the kidney and ureters may be missed by ¹¹C-HED PET/CT. Moreover, the high physiologic liver uptake may hinder the detection of small liver metastases.^{59,100} Finally, another important limitation is

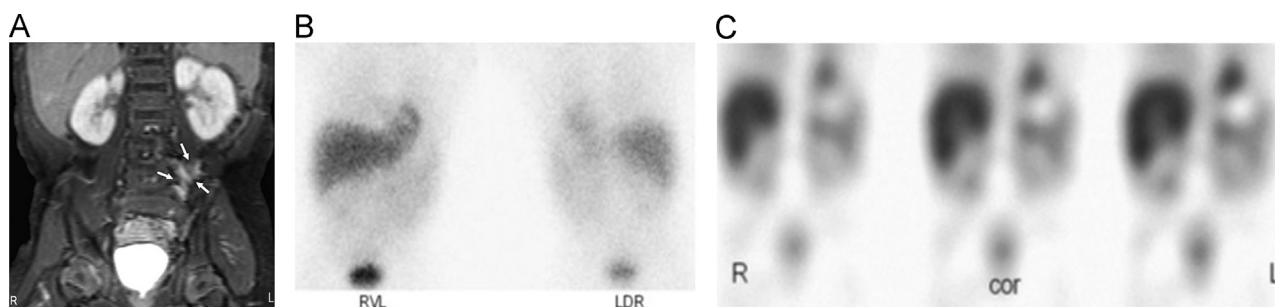


Figure 6 A 2-year-old boy with reactive changes 1 year after resection of stage III neuroblastoma. (A) Paravertebral contrast-enhancing mass (arrows) is visible on T1-weighted image. Differentiation between residual tumor and reactive changes is not possible with MRI (false-positive finding). (B) Planar ¹²³I-MIBG scintigrams reveal true-negative finding. RVL, right side, ventral view (left); LDR, left side, dorsal view (right). (C) Coronal (cor) SPECT reconstructions of ¹²³I-MIBG scintigraphy support negative finding of planar images (B). True-negative diagnosis was confirmed by biopsy and follow-up control examinations over 2 years.

related to the short half-life of ^{11}C , which requires an on-site cyclotron and a rigid time schedule.

^{124}I -MIBG

To the best of authors' knowledge, no clinical pilot studies on the diagnostic role of ^{124}I -MIBG PET/CT in NB are available, but one case study was published recently on this issue.¹⁰¹ Cistaro and colleagues reported two cases of children affected

by metastatic NB scheduled for ^{131}I -MIBG who underwent ^{124}I -MIBG PET/CT after MIBG treatment. In this series ^{124}I -MIBG PET/CT identified the same NB lesions detected by high dose posttherapy ^{131}I -MIBG scan. In addition, ^{124}I -MIBG PET/CT provided more accurate evaluation of disease extension in one patient affected by spine metastases with intraspinal and extraspinal involvement.

The authors suggested performing ^{124}I -MIBG PET/CT as a pretherapy examination, given the high diagnostic accuracy, and for restaging, especially when doubtful

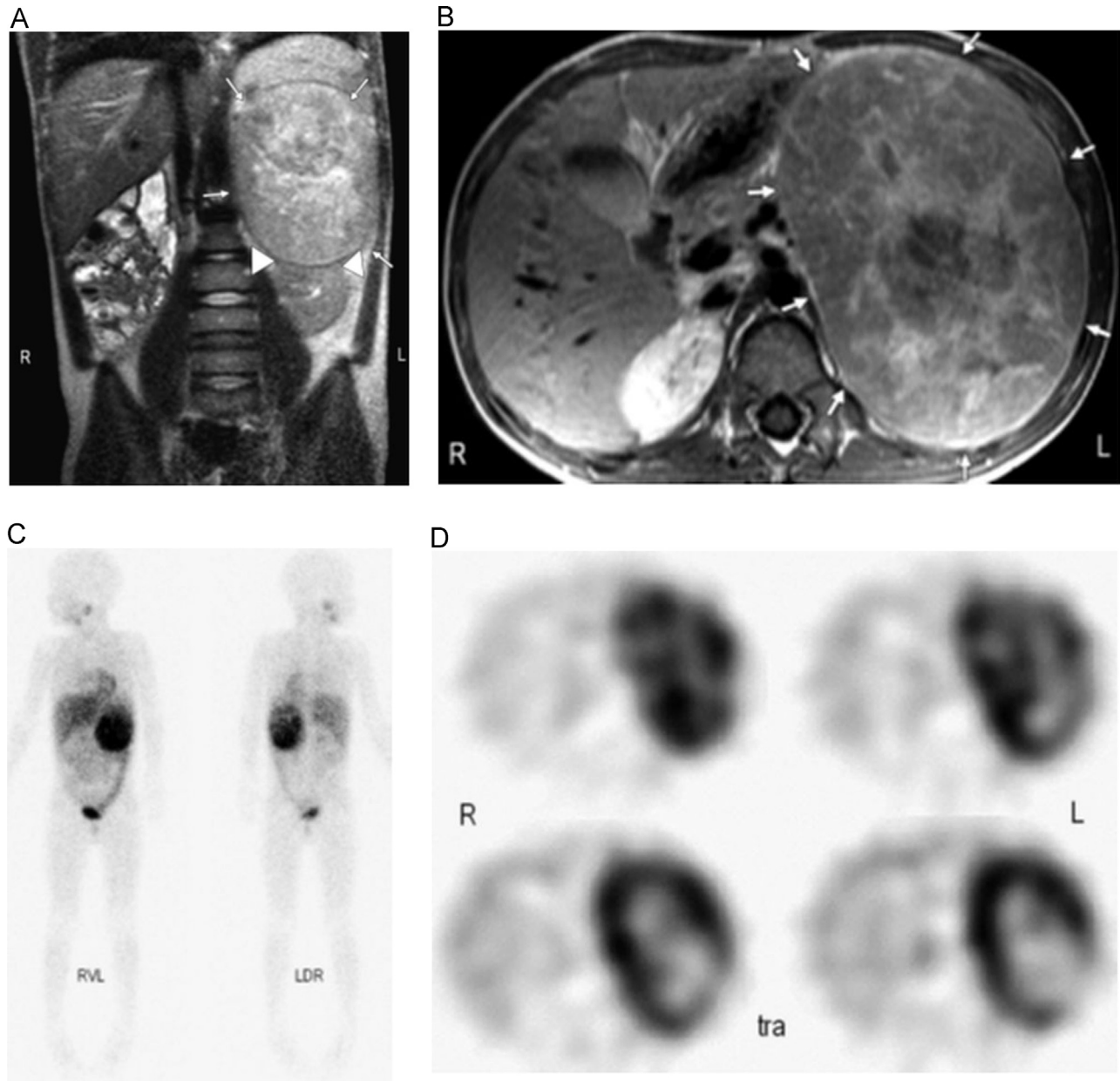


Figure 7 A 6-year-old boy with large neuroblastoma originating from left adrenal gland. (A) Coronal T2-weighted image reveals large mass in left abdomen (arrows) with appearance typical of Wilms' tumor with pseudocapsule and apparent origin from kidney (arrowheads) (false-negative finding regarding diagnosis of neuroblastoma). (B) Corresponding transverse T1-weighted image depicts large mass (arrows). (C) Strong focal uptake by mass visible on ^{123}I -MIBG scintigrams led to correct differential diagnosis of neuroblastoma (true positive finding). RVL, right side, ventral view (left); LDR, left side, dorsal view (right side). (D) Transverse (tra) SPECT reconstructions that correlate to MRIs show tumor extent and central tumor necrosis.

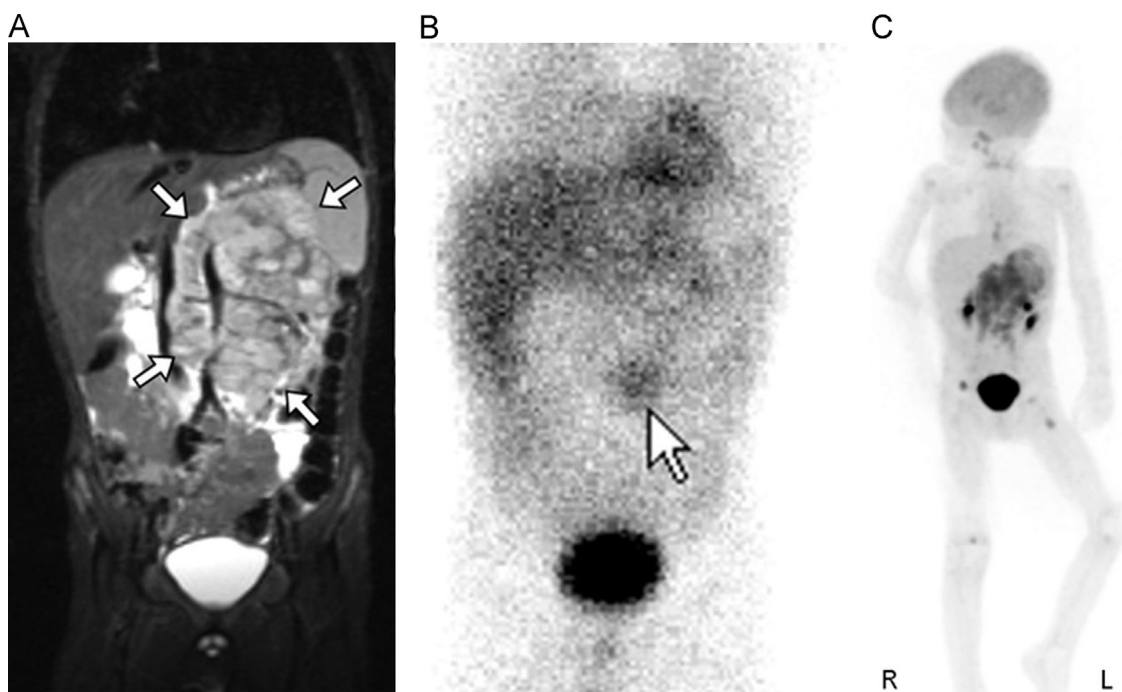


Figure 8 A 3-year-old boy with a large midline-crossing abdominal neuroblastoma. (A) Coronal T2-weighted MR-image depicts large primary tumor in abdomen surrounding the abdominal aorta (arrows). (B) Corresponding planar images of ^{123}I -MIBG scintigraphy only show increased uptake in the central part of the primary tumor or physiological uptake of the bowel (arrow). The residual mass is MIBG-negative. (C) Maximum intensity projection of FDG-PET shows hypermetabolism in the entire primary tumor as well as in multiple bone metastases that could not be visualized with MIBG scintigraphy. L, left side, R, right side.

findings are evidenced by scintigraphic imaging with ^{123}I - or ^{131}I -MIBG.¹⁰¹

Beyond this very limited clinical experience, ^{124}I -MIBG represents several advantages in image quantification, radionuclide characteristics (^{124}I half-life of 4.2 days, that is, more similar to the 8.02-day half-life of ^{131}I), and whole-body PET acquisition,¹⁰² that can be well exploited for both diagnostic imaging and dosimetry.

In the clinical setting, ^{124}I -MIBG has been used for dosimetric purposes since the early 1990s.¹⁰³⁻¹⁰⁵ Lee et al¹⁰⁴ reported that ^{124}I -MIBG is significantly more advantageous than other ^{124}I compounds, especially ^{124}I -NaI, and that the estimated effective dose of ^{124}I -MIBG is more than ten times lower than that of ^{124}I -NaI (0.25 mSv/MBq radiation dose estimated for ^{124}I -MIBG, vs 6.5 mSv/MBq for ^{124}I -NaI).

However, these effective dose values are 10-fold higher than those obtained with ^{123}I -MIBG (0.019 mSv/MBq)^{102,104} and have a significant relevance in the pediatric population, when ^{124}I -MIBG PET is used for diagnostic purposes. Therefore, the authors recommend administering of low doses, especially in small children, and suggested that the best indication for ^{124}I -MIBG PET is pretherapy dosimetric study before ^{131}I -MIBG treatment.¹⁰²

Nevertheless, the improved characteristics of modern PET/CT scanners allow limiting the administered dose while maintaining an adequate image quality. Moreover, the additional dose can be considered negligible when ^{124}I -MIBG is performed as a pretherapy evaluation tool before ^{131}I -MIBG treatment.¹⁰¹

More extensive investigation of ^{124}I -MIBG is needed before defining the correct use of this tracer in NB patients.

Morphological and Multimodality Imaging

The major limitation of morphological imaging (CT/MRI) is the assessment of the viability of morphologically detectable lesions. On the contrary, functional imaging (MIBG/PET) often lacks in distinguishing physiological changes vs tumor lesions. In this concern, multimodality imaging can help to increase diagnostic safety for defining the adequate therapeutic consequence.

In contrast to CT, MRI has several advantages in the diagnosis of NB—high sensitivity in detecting bone marrow abnormalities,¹⁰⁶ lack of ionizing radiation, high intrinsic soft tissue contrast resolution,¹⁰ depiction of internal structure,¹⁰⁷ and exact definition of intraspinal tumor extension or diaphragmatic involvement of thoracic tumors.^{9,108} All these factors are decisive, especially in primary diagnosis and for operative or biopsy planning.¹⁰⁹ In a comparative study, Pfluger et al⁴⁴ assessed the benefit of a combined analysis with MRI and MIBG scintigraphy in pediatric NB lesions. In this study, MIBG scintigraphy, MRI, and combined analysis showed a sensitivity of 69%, 86%, and 99% and a specificity of 85%, 77%, and 95%, respectively. On MRI,

15 false-positive findings were recorded: posttherapeutic reactive changes ($n = 10$) (Fig. 6), benign adrenal tumors ($n = 3$), and enlarged lymph nodes ($n = 2$). On MIBG scintigraphy, 10 false-positive findings occurred: ganglioneuromas ($n = 2$), benign liver tumors ($n = 2$), and physiologic uptake ($n = 6$). Total 13 NB metastases and two residual masses under treatment with chemotherapy were judged to be false-negative findings on MRI. Two primary or residual NBs and one orbital metastasis were misinterpreted as Wilms' tumor (Fig. 7), reactive changes after surgery, and rhabdomyosarcoma on MRI. Total 32 bone and bone marrow metastases, 6 other NB metastases, and 1 adrenal NB showed no MIBG uptake (Fig. 8). On combined imaging, one false-negative (bone metastasis) and three false-positive (two ganglioneuromas and one pheochromocytoma) findings remained. In conclusion, MRI showed a higher sensitivity and MIBG scintigraphy a higher specificity. However, integrated imaging showed an increase in both sensitivity and specificity.⁴⁴

Rozovsky et al¹⁶ reported on the added value of ¹²³I-MIBG SPECT/CT compared to contrast-enhanced CT scan in eight children with NB. They observed that all equivocal cases on CT were solved by SPECT/CT, related to the high specificity of ¹²³I-MIBG for tumoral tissue, and concluded that during follow-up of children with MIBG-positive NB at diagnosis, SPECT/CT should be performed first and, if negative, contrast-enhanced CT could be discarded. Inversely, single positive or equivocal MIBG foci without concordant morphological changes may need histological confirmation.¹⁶

Conclusions

There is strong evidence that ¹²³I-MIBG scintigraphy (planar images and SPECT) remains the method of choice for the noninvasive staging of children with NB. PET imaging using FDG or the more specific tracer FDOPA has not proven to be superior to MIBG. However, data in the literature indicate FDOPA to be the most promising PET tracer with the potential to replace MIBG scintigraphy in the diagnostic work-up of NB in the future. The indication for FDG-PET/CT is given in all cases with discrepant findings in functional (MIBG/FDOPA) and morphological (CT/MRI) imaging (Fig. 8).

Regarding multimodality imaging, it has been shown that a combined approach with MIBG/MRI, MIBG/CT, and PET/CT has the potential to increase diagnostic sensitivity and specificity as compared to single modalities.

Concerning the state-of-the-art diagnostic strategy in NB imaging, it is important to differentiate between primary diagnosis and follow-up controls.

In primary diagnosis, MIBG scintigraphy/FDOPA PET/CT (ie, whole-body staging, differential diagnosis) and MRI (ie, operability, bone marrow metastases) are indispensable.

In follow-up examinations, MIBG scintigraphy (FDOPA PET/CT) is most important, as specificity of morphological imaging is very low here.

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